PPTA
Plasma Protein Therapeutics Association

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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

VIA E-Mail & USPS

SUBJECT: Public Workshop, "Development of Plasma Standards." July, 2005.
Docket No. 2004N-0539.

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) and its member companies appreciate the Food and Drug Administration's (FDA) providing a docket to receive comments to its Public Workshop entitled, "Development of Plasma Standards" [Hereinafter "Workshop"], held on August 31-September 1, 2004 on NIH Campus in Bethesda, Maryland. PPTA is pleased to provide comments and thanks FDA for its careful consideration of written comments, as well as, industry participation in the Workshop. PPTA's comments highlight the most critical areas of importance to our industry as noted in our Executive Summary.

Executive Summary

- PPTA favors science-based regulations as a foundation for international harmonization.
- The quality of the finished therapeutic product depends on the totality of a complex manufacturing process, containing numerous important specifications detailing the parameters of a quality process, none of which can be evaluated in isolation.
- Regulatory standards should add measurable value to the margin of safety for a product.

Within the context of these primary areas of concern, we are providing detailed comments below.

Background: The Regulatory Landscape

The regulatory structure of both the United States and the European Union are predicated on efforts to promote patient safety and product quality. While the aspects of safety and quality are inextricably intertwined, plasma products carry higher levels of safety and quality now than ever before. In all of the discussion of these temperature and timing issues, not a single instance of a problem with patient safety or a difficulty with product quality has been cited by the Agency.

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Interest in issues of plasma storage and freezing have come about as the Agency has directed its attention towards setting standards for recovered plasma, a starting material for fractionated therapies that has been handled via short supply agreements (21 CFR 601.22) and has remained essentially undefined from a regulatory sense. Aside from certain labeling requirements, recovered plasma is regulated only indirectly by the regulations addressing the transfusible component from which it is "recovered." The other starting material for fractionated therapies, Source Plasma, is a licensed product regulated primarily under 21 CFR §640.60, et seq. Despite the differences in the regulatory approaches to control of starting materials, fractionators can and do make products from these raw materials that are consistently safe and effective, and the products manufactured by PPTA member companies have an excellent track record for safety and efficacy using either Source or recovered plasma. Indeed, these products are among the safest on the market.

The issue of whether recovered plasma needs controls beyond "short supply" is not a new issue but has been considered by the Agency periodically over the years. In this most recent consideration, the Blood Products Advisory Committee (BPAC), at its June 2003 meeting, heard proposals from the Agency and other parties regarding a licensing scheme for recovered plasma. As the Agency has focused on recovered plasma standards, it has also included comparisons of the different types of human plasma used in the manufacture of therapeutics and, in some cases, diagnostic devices. The presentations given both by Agency staff and representatives of the Source Plasma and whole blood industry sectors at the June 2003 BPAC meeting displayed a spectrum of opinions regarding potential areas of consideration in changing the regulatory requirements to address the concerns about raw material inconsistency. A part of the reason why so many varying views were expressed was that the discussion centered on a highly complex and nuanced situation when comparing the regulatory schemes and business practices in place for the whole blood and plasma collection centers. The discussion disclosed the difficulties inherent in changing long-standing regulations, not only from the standpoint of business practices and procedures built on the regulations, but even in drilling down to the reasons behind the regulations. The center of the question about appropriate regulations, still not easily understood nor completely resolved, lays on the definition of the product in question, with elements such as intended use, proper freezing, dating periods, and so on. Issues surrounding the perceived disconnect between regulatory requirements for recovered plasma and Source Plasma, nomenclature of the plasma, and freezing issues were all considered by the members of BPAC.

Despite some deep confusion about several of these issues and concerns, the BPAC meeting was followed by a Proposed Rule released by the Agency later that summer. The Rule outlined changes relating to blood component labeling, but also proposed changing the storage temperatures for Source Plasma collection facilities. At the time, the Agency stated the belief that these efforts in the Proposed Rule would aid for industry harmonization.

In comments submitted to the FDA docket on October 28, 2003, PPTA detailed several areas of difficulty with the Proposed Rule issued by FDA in July of 2003. (See Docket No. 2003N-211, PPTA Letter, Reference Number FDAA03011). The Proposed Rule was issued

under Federal Register Notice Vol. 68, Number 146, pp. 44678-44688. Contained in those extensive PPTA comments to the Proposed Rule was a critique of the scientific basis cited by the Agency as operative for altering the storage temperature from -20°C to -30°C, an economic analysis of the impact of the proposed rule, and other areas germane to the FDA's decision to amend the language prior to issuing the Rule in final form.

PPTA's basic concerns are ones still shared by the industry, albeit the issue has shifted from storage temperature to freezing temperature and rate of freezing. In terms of the PPTA comments to the Proposed Rule, the industry calculated that the costs of the Rule to the industry would likely have exceeded $70 million. In addition to these costs, the scientific basis cited by FDA supporting the regulatory changes were not truly reflective of true-to-life plasma collection conditions, nor did the supporting studies truly simulate the needs of a modern manufacturing process. The changes also would have required other changes, in areas such as environmental health and safety requirements and considerations.

After closure of the Docket relating to the Proposed Rule, FDA officials have stated on numerous occasions that the portions of that Proposed Rule relating to storage temperatures will not be pursued, but that areas of agreement, such as the labeling portions, will be finalized at some point in the future.[1] Informal means of communication have also indicated that the storage temperature proposal will not be pursued; however, the Agency maintains a continued interest in plasma quality, including collection and handling practices.

The Workshop was undertaken by FDA in an effort to obtain information on current industry practices with respect to freezing, storage and shipping of plasma, review scientific data, and global regulatory requirements with the view to potentially harmonize requirements with other regulatory bodies. FDA's further stated objective for the Workshop was to ensure that regulatory decisions are based on science, need and practicality.

The Importance of Science-Based Regulations in Harmonization

PPTA agrees with FDA's stated objectives and has long supported the concept of science-based regulatory harmonization. At the Workshop, the scientific basis of previous regulatory efforts and the scientific questions being considered by Workshop participants were ably summarized by Dr. Albert Farrugia of Australia's Therapeutic Goods Administration. Dr. Farrugia's highly detailed and exhaustive review of the current state of scientific knowledge brought up legitimate inquiries and also exposed a critical need for a consensus view on the temperature issues. Dr. Farrugia detailed several of the conflicting findings in the scientific literature and also noted the age of some of the publications; in some cases, the publication data of the studies was more than twenty years ago. In this sense, one could make an argument favoring more detailed, updated studies. On the other hand, one can point to the dated literature and the foundations of the regulations, and the long history of a manufacturing process that create safe and efficacious therapies, and

[1] Dr. Jay Epstein, Director of CBER-OBRR, stated at this very workshop that freezing temperature is still a viable area for discussion, while storage temperature is not likely. See Transcript, p. 194.

legitimately question the need for re-opening a long-settled area of regulations that have served, and continue to serve, patients and industry both. These patient populations are served around the world by global companies that depend upon stability of regulatory structure and the scientific basis of the regulations.

One of PPTA's goals, often publicly stated, is that of international harmonization. In today's global marketplace, standards imposed by governments should, whenever practicable and safe for the population, be based on science and necessity, least burdensome for compliance, and compatible with other governments' standards. Absent compelling public health reasons, for example, a non-harmonized regulation could be construed as possessing a primary purpose of trade protectionism, rather than as a bulwark for public health and welfare. National or regional public health and medicinal product licensing authorities, therefore, have a responsibility to protect their respective populace, but also a responsibility to ensure that regulations and standards are tailored to the ends of protecting the public health without causing an undue burden on international trade, as secured by international agreement and force of law. More commonly, standards designed to protect public health through different means, while not rising to the level of a protectionist measure, still have quantifiable and significant impact on an industry seeking to market a product in several jurisdictions.

Automatic adherence to any strictest standard without a scientific basis would not be true harmonization. True harmonization requires an understanding of the scientific underpinnings and practicability of the regulatory proposal; the harmonization effort is therefore an exercise in optimization first and is consensus driven. Relevant questions pertaining to harmonization are targeted to resolve issues regarding optimization and compatibility and an understanding of other regulatory processes faced by industry when marketing safe and effective therapies.

Specific U.S. and European Requirements

In terms specific to the issues discussed at the Workshop, storage and freezing temperatures for plasma products, there are differing standards between the U.S. FDA and European regulatory authorities. For Source Plasma, the bulk of the regulations for licensure are contained in 21 CFR §§640.60-640.76 in the United States and, in the E.U., the requirements are coded in European Pharmacopeia Monograph 0853, *Human Plasma for Fractionation.* It is important to note that PPTA, in these comments and in previous communications, did not consider the non-legally binding documents for transfusible products, Recommendation No. R(95) of the Council of Europe. Instead, PPTA will focus on the EP Monograph and the pertinent CFR sections, as these are the documents that have binding, legal effect.

Comparison of the two requirements for Source Plasma discloses the following:

	US[2]	European Pharmacopoeia		
Purpose	Source plasma	Labile proteins for fractionation	Non labile protein for fractionation	Non labile protein for fractionation
Collection method	Plasmapheresis	Plasmapheresis Or Plasma from whole blood	Plasmapheresis	Plasma from whole blood
Time from collection to freezing	Immediately	**≤24 hrs**	**≤24 hrs**	**≤72 hrs**
Freezing conditions, temperature	≤-20 °C	**Chamber at ≤-30 °C**	Chamber at ≤-20 °C	
Storage, expiration	≤-20 °C, 10 yr	≤-20 °C		
Shipping temperature	≤-5 °C	**≤-20 °C**		
Allowable deviation	> -20 °C for ≤ 72 h total Never > -5 °C, always frozen	> -20 °C for ≤ 72 h total One time > -15 °C, Never > -5 °C		

Clearly, as illustrated in the table above, there are differences, in terms of freezing temperature, the time to freezing, and the concept of having a shipping temperature in addition to a storage temperature. The latter concept may indeed be one that warrants more discussion. Freezing as a concept has had different interpretations as well, among *and* within the jurisdictions. For example, historically, the EP requirement of freezing at a temperature has not been interpreted as freezing *to* -30°C but, instead, freezing in a chamber *at* -30°C. The difference between those two modifiers is a large one.

Similarly, the difference in timing of freezing, or placement in the freezer, is significant. The United States standard is interpreted as a thirty-minute ceiling after collection, while the European standard is more permissive with the 24-hour requirement.

The question thus resolves into this: do the existing standards need further adjustments...or are the standards compatible as is?

With the long U. S. history of plasma collection and fractionation, the use of short-supply agreements for recovered plasma and the licensing of Source Plasma have provided a firm foundation for the raw materials used in further manufacture of plasma-derived products. Fractionators can and do specify additional criteria, in addition to the regulations; these additional specifications play a role in the individual and proprietary manufacturing

[2] Table presented by Dr. Mark Weinstein, FDA-CBER, PPTA Plasma Protein Forum, June, 2005.

processes used by the brand manufacturers and are not suitable for inclusion as a regulation of general applicability.

As mentioned above, the EP monograph provides a distinct set of regulations that differ somewhat from the United States CFR. While these requirements may appear to be ripe for harmonization, the view of the industry is that companies which have a stream of commerce leading to the European market use the European specifications. Companies that do not market in Europe do not use those standards; instead, they use those specified by the CFR. And, in the absence of a product safety or efficacy issue, the EP and U.S. regulations have reached a point of near-harmonization already, with some highly desirable flexibility included. Further efforts to "harmonize" these requirements will lead to a loss of that flexibility and would not be beneficial to patients or the industry.

Harmonization efforts should be focused on areas of inefficiency and any regulations springing from those efforts should be science-based; by definition, these harmonization efforts are consensus-driven by government agencies, industry, and patient groups. In turn, this consensus should be based on patient safety and sound science. This becomes especially clear when there is unanimous agreement among the regulated industry that these issues of temperature are of extraordinarily low priority.

The Finished Therapeutic Product

Dr. Daniel Albrecht, ZLB Behring, offered several important points in viewing the fractionation industry, the recipient of the raw material and customer for the plasma collection industry. Plasma used for fractionated products is subject to a manufacturing process which, on one hand, inactivates known pathogens, such as HIV, HCV, and others. Secondly, the manufacturing process itself, by function of being engineered to create quality products, ensures a high degree of consistency in the finished product. Therefore, the finished product, regardless of the raw material collected, is subject to a manufacturing process which protects patients against the potential infectious disease transmission by the product and also allows patients to have a product that has a high degree of consistency and efficacy in treatment. These processes, in their totality, ensure safety and efficacy with either Source or recovered plasma, when those raw materials meet *basic* requirements, of which freezing and storage practices are one. Basic, in this sense, means both foundational and non-specific, in that while the temperatures are fundamentally important, one temperature or freezing practice is not so superior that it would have a value-added, positive impact on the process as a whole. So long as the raw material meets an elementary standard of suitability for use in the carefully-designed process, the temperature requirement is satisfied. Thus, the question of use of a specific type or brand of raw material becomes a *business* decision, best left to the individual businesses. It is not a safety issue, nor an efficacy issue. So long as the basic requirements of safety and efficacy are met, the regulations establishing the foundational aspects of safety should remain unchanged and not be bent to accommodate a specific practice.

The industry does have complex internal relationships. Fractionators may trade intermediates and pastes. Fractionators may use both Source Plasma and recovered

plasma. Blood banks and plasma collection centers may be under contract with a number of fractionators. And yet, despite these complex relationships, the end product is imbued with a high degree of quality, ensured through a process governed by several different quality systems, including industry standards, European regulations, and the U.S. Code of Federal Regulations.

Dr. Albrecht posed the question, after reviewing the manifold quality and delivery requirements presently in the normal course of business in the plasma industry: "Do we [need] to develop additional standards for the preparation, labeling, storage, and shipping of plasma in order to ensure the safety, purity, and potency of the therapeutic[] products?"

The Manufacturing Process & Specifications

In answering this query, and building on what was mentioned above, one must view the manufacturing process, its controls, and its specifications, as a whole. Specifications play an important role in the totality of the biological product manufacturing process. This process incorporates a strategy ensuring that products are consistent, safe, and efficacious. Such a comprehensive strategy uses in-process controls and testing, control of the raw materials, continuous monitoring of the manufacturing process, and cGMP compliance. After the process, the product is tested by characterization, release, and stability protocols. All of these individual parts of the process help give confidence to the manufacturer, patient, and regulatory body that the products are safe and efficacious. All specifications are intertwined with the process. According to the International Conference on Harmonization, "Specifications establish the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use."[3]

It is, however, a fundamental error to assert the importance of a single specification without viewing it in the context of the total manufacturing process and the complete quality control paradigm. Measurement of product quality, a test or a specific analytical procedure, for example, depends upon the complete process. As such, altering a comparatively minor specification such as temperature or rate of freezing, by regulatory fiat alone, unsupported by scientific evidence, would most likely have no positive reflection on final product quality. In this way, establishing a regulatory standard for a specification represents for the industry considerable resource expenditure and a reduction in valuable manufacturing flexibility, with no measurable benefit to patient safety or product efficacy.

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[3] ICH Harmonised Tripartite Guidance Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, cited by Dr. M. Marcia Federici, GlaxoSmithKline, "A Perspective on Specifications for Biotechnology Products", presented at American Association of Pharmaceutical Scientists Workshop: *Specifications for Biotechnology and Biological Products*, October, 2004, Washington D.C. Dr. Federici also stated that the Pharmaceutical Research and Manufacturers of America have interpreted this standard to mean: "One product, one process, one set of specifications." This interpretation, which correctly reflects the scientific and engineering details of the manufacturing process, underscores the difficulties that industry will encounter when manufacturing a varied product portfolio from the same liter of raw material and losing the flexibility required to do so.

Indeed, focusing solely on the freezing temperature or rate predicated on a single product, plasma-derived Factor VIII, ignores both the practical aspects of the engineering principles of specification setting and the realities of the economics of the plasma industry. The former is discussed above; in the case of the latter, harmonization based on scientific criteria and principals, help generate new efficiencies in the global market that benefit patients. Every new, more stringent regulation that eliminates flexibility entails costs that are diverted from areas of critical concern, such as pathogen research, innovation and new product development, and the increasing cost pressures of reimbursement and raw material prices.

A question raised at the workshop was whether labeling requirements for plasma should include stratification based on collection practices, time to freezing, temperature of freezing, and storage temperature. The industry views that the current statement of minimal requirements is sufficient. Currently, specifications beyond the regulatory requirements are stated in contracts between the fractionator and the plasma supplier. Those specifications are generally reflected in company-specific product codes. The current framework is satisfactory and does not require further regulatory intervention.

Freezing, as an action pertaining to the quality chain of plasma therapeutic manufacture, has several factors which can impact performance: freezer size, the external environment, freezer load, collection center volume, and heat exchange over time. One does not "adjust" freezer temperature in a plasma center. If a freezer is set for a certain temperature, say -28°C, one does not twist a rheostat to squeeze two more degrees out of the machinery. The entire device requires careful construction, monitoring, and validation. Changing a standard upon which these complex mechanisms have been designed –and the business practices in turn—is a serious matter that goes beyond conventional understandings of freezers and refrigeration. We reference Mr. Jim Viane's presentation from the Workshop, which details the massive shifts and costs that would be incurred by industry to effect the change in regulations...and to an end which is not clearly defined, a purpose that is not explained, and an issue that does not improve the overall quality of the product portfolio, or the manufacturing process behind the therapies.

Dr. Albrecht concluded that today's standards are indeed satisfactory for modern products, answering his question, reiterated above, in the negative. We agree with Dr. Albrecht that both industry and FDA should focus attention on areas of the greatest need and likelihood for the greatest positive impact on patient safety. FDA's many new initiatives, such as the risk-based approach, Pharmaceutical GMPs for the 21st Century, and the Critical Path, all pose important opportunities in which the industry and Agency can partner to effect these positive changes. Possible considerations for changes toward harmonization abound: serology testing, acceptance of software, anticoagulant usage, donor fingersticks, lookback periods and deferral requirements, and others. Harmonization efforts should be dedicated toward measures that add value in terms of patient and product safety through the use of best practices. Temperatures and freezing practices, once reaching a certain general level of acceptability, do not add to patient or product safety.

The presentations given by the individual companies show the extent to which industry specifications are uniform. More importantly, it demonstrates that small differences in terms of the raw materials do not have a substantive impact on product safety or efficacy. The most important touchstone in examining these specifications and review of the fractionator processes is *whether patient safety is an issue.* Clearly, while patient safety is of the highest concern, there are no patient safety issues that can be linked to the freezing and storage practices of the plasma collectors.

The presentations showed near-uniformity of practice in the areas cited by the Agency as being of the greatest concern. The specifications set are shared by nearly all companies, with only slight variations in terms of handling and shipping and reflect the business practices of the manufacturers, primarily in terms of whether a given product is marketed in Europe or in the U.S.[4] One company requires freezing and storage only to the standards contained in 21 CFR §640.69(b),[5] specifically freezing and storage at -20°C rather than freezing at -30°C and storage at -20°C.

The freezing rate and temperature debate appears to have taken a life of its own, with no real connection to any current manufacturing issues. It is, therefore, a solution in search of a problem. Implementation of temperature and freezing practices standards without due regard for the engineering and scientific realities in a modern manufacturing process would lead to disharmonization, a loss of flexibility, increased costs, and no benefit to patient safety.

The Workshop and the Value-Added Paradigm

Discussions regarding such standards must not only be held, but careful crafting must be done to ensure adequate communication of the perceived need for regulation, and the value to be created in further development of the regulatory scheme. An important consideration in any business or policymaking decision, including a regulatory measure, is the feasibility and value of such a measure. No one would reasonably argue about costs in the face of an issue regarding loss of product quality or, even more importantly, a decline in the safety profile of a therapy. In considering these issues, as compared to the concerns outlined above with regard to patient safety (or, in the instant discussion, lack of an issue related to patient safety), policymakers and industry should be in agreement as to the value gained in terms of safety. If there is indeed an issue regarding safety, and safety can be improved, industry is prepared to consider costs. If, however, there is no patient safety issue, no therapeutic efficacy issue, and only increased costs without a concurrent gain in safety, then the paradigm becomes one of a negative sum, with only costs incurred and no improvement to justify the expenditure. Thus, there is no feasibility or relative value to such a measure.

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[4] See presentations by Roger Brinser, Baxter BioLife, James Sesic, Grifols Pharmaceuticals, Barbara Glantschnig, Octapharma, and Jonathan Knowles, Dr.P.H., ZLB Plasma Services

[5] See presentation by Mary Ann Lamb, Ph.D., representing Talecris Biotherapeutics, Inc. (formerly Bayer HealthCare).

The Agency noted that the Workshop is an example of an effort of the public process to be undertaken to provide some "minimal standards" in the area of freezing and handling of plasma. There has not been, however, any indication of an articulable basis of a need for minimal standards beyond the current requirements. PPTA member companies' products have been of consistently high quality, safety, and consistency, and no patient group appearing at the Workshop expressed any concern about the safety and efficacy of the therapies.

The plasma industry agrees with many of the points made by Dr. Donna DiMichele, in her presentation entitled "The Need for High Quality Plasma Derivatives." In that presentation, Dr. DiMichele stressed, among other issues, the importance of a harmonized approach to industry regulation and the need for a clear understanding as to the economic structure of the global plasma industry. This economic structure is rooted in a production entity's need for a balanced product portfolio; it is no longer possible for a corporation to support itself by producing a single product from collected plasma.

To this end, the marketplace favors efficient plasma fractionators that possess a balanced product portfolio. While yields remain an important factor in consideration for a fractionator evaluating the raw materials (i.e., plasma collected either from whole blood or from plasma apheresis donors), tests based on levels of a single protein do not disclose the information that a manufacturer needs to make a binary determination of "acceptability." In short, Factor VIII levels do little to help a fractionator determine the "quality" of a plasma unit, *because of* the need for the balanced product portfolio. A handful of studies, several decades old, do not provide an adequate scientific basis on which a regulatory standard, however "minimal" it may be termed, can be based, especially given the differences and contrasts between industrial-scale production and laboratory techniques. Altering a parameter involving freezing practices, absent a patient safety issue and a clear linkage to the specification, is not a value-added activity.

Recovered Plasma Issues

The AABB has a long history as a well-respected industry organization and as a standard-setting entity. The AABB Recovered Plasma standard, and the AABB Task Force responsible for it, represents a possible methodology which the Agency may choose to use to resolve some questions it may have about licensure of recovered plasma. The original distinction between Source and recovered plasma came about as a result of a separation based on collection frequency and donor demographics and profiles. Because the industry has a more unified outlook now, and with the advent of international standards and trade globalization, a more harmonious approach is desirable. In this regard, the AABB standard may be incorporated by the Agency by altering some of the definitions contained in the Code of Federal Regulations; namely, §640.30(a), to include manufacturing as an intended use. The AABB standard, if used as a basis for regulation, should help harmonization efforts.

Thus, PPTA supports the efforts of AABB in its Task Force's recommendations regarding recovered plasma. PPTA believes that certain definitions within the Code of Federal Regulations would need minor amendment to accommodate the AABB suggestions, and will allow the regulatory definition of Source Plasma, contained at 21 CFR §640.60 to remain unchanged and will continue to provide a firm basis upon which the Source Plasma collection industry has been operating from.

Nonetheless, PPTA cautions against the use of overly specific regulations. An example of this can be found in 21 CFR §640.69(b) and is mentioned above as well: the requirement that Source Plasma be immediately removed to a freezer after the collection bottle is filled. This absolute and unachievable regulation has been re-interpreted on several occasions to make Source Plasma storage practicable. This has been achieved through the use of modifying terms found in the Guide to Inspections, stating that the storage practices should be performed "without undue delay." This has been further re-interpreted as being a time period of thirty minutes.

The evolution of the requirement, from "immediately" to "within 30 minutes," is an example of an area where an absolute metric has little meaning. While we understand the importance of having a standard set up to ensure product safety and efficacy, it is difficult to see that a unit of plasma left at room temperature for 31 minutes is inferior to a unit left at room temperature for 29 minutes. This *reductio ad absurdum* may be seen as quibbling about a standard, but we use it as an example of a metric that should not be emulated in any future rulemakings or Guidance Documents on this issue.

Conclusions and New Directions

Over the past eighteen months, the FDA has been quite active in promoting new regulatory paradigms and new methods and paths to licensure for discussion with industry, for new drug development, accelerated approval, and enhanced safety and efficacy. Examples of these paradigms are the Critical Path Initiative, Process Analytical Technology, cGMPs for the 21st Century, and so on. As PPTA noted in its presentation at the *Workshop on Intravenous Immuneglobulins in the 21st Century: Progress and Challenges in Efficacy, Safety, and Paths to Licensure,* held on April 13, 2005, the current difficulty can best be understood in terms of inertia. We stated at that meeting, the FDA's work in bringing new regulatory concepts to light has been excellent, but it is also difficult at times for an industry to understand the value added by these new programs, in comparison to current business practices. It takes investment in resources and time to change current practices and without a clear picture of the advantages of these new programs, it may be more desirable for a manufacturer to continue in its current practices, especially when the value and objectives of the new programs are not clear.

To facilitate greater acceptance of these new possibilities, PPTA is interested in meeting with FDA officials and hearing, in greater detail and with greater specificity for the plasma industry, the opportunities generated by these exciting new programs. PPTA's member

companies are interested in pursuing prospects that enhance patient safety and product quality.

While our industry is, right now, puzzling over some of the possibilities that the Critical Path and other programs do indeed represent, several things are clear. One, the programs such as Critical Path do offer a route ahead to improving product safety and efficacy, and creating a regulatory program which facilitates, rather than discourages, product development. Encouragement of innovation is closely correlated with regulatory paradigms and understandings of the current business climate, which includes a total view of the industry and a complete understanding of modern manufacturing processes. Also, the new FDA programs appear to view the manufacturing process in its totality, as opposed to singling out regulatory standards of comparatively minor importance.

Dr. Celso Bianco of America's Blood Centers made a statement that succinctly –and legitimately—explained much of industry's confusion about the Workshop: "Why are we here?" We have seen demonstrated, through earlier comments, through public statements, through earlier statements contained in this Docket submission, and most importantly, through our industry and the patients served, that plasma products are safe and efficacious. We have shown that the freezing practices, while important, cannot be viewed in isolation, abstracted from the complex manufacturing process in its entirety. We have studied the scientific basis cited by the FDA for changing these standards and have found it wanting. In the absence of a patient safety issue, in the absence of a product quality issue, industry is puzzled by the level of concern expressed by the Agency on these issues.

As mentioned above, a single parameter within an entire process will not likely result in an improvement to the process. Each specification and subroutine in the manufacturing realm must be taken in the context of the finished product and the process which creates it. The massive costs associated with changing these temperature requirements, only to have no measurable positive effect on the manufacturing process, clearly results in a less-than-zero-sum game.

Changing the freezing temperature and freezing rate are not regulatory initiatives that would comport with the other forward-looking programs the FDA is currently touting.

We look forward to discussing value-added initiatives with the Agency. If you have any questions or need clarification of any of the issues raised in these Comments, please contact us at the Association offices. PPTA again thanks the FDA for the opportunity to participate in and comment on the Workshop on Plasma Standards.

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in

emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

Respectfully submitted,

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